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(54) Titre : SYSTEME THERAPEUTIQUE TRANSDERMIQUE HAUTEMENT FLEXIBLE RENFERMANT DE LA NICOTINE EN TANT QUE SUBSTANCE ACTIVE

(54) Title: HIGHLY FLEXIBLE TRANSDERMAL THERAPEUTIC SYSTEM HAVING NICOTINE AS ACTIVE SUBSTANCE

(57) Abrégé/Abstract:
The invention relates to transdermal therapeutic systems having nicotine as active substance, which are characterized by a particularly high flexibility. Said flexibility decisively improves carrying comfort on the skin due to the fact that the system can easily adapt to the surface of the skin and its continuos movement. The nicotine TTS according to the invention is clearly more flexible than leading nicotine TTS products currently available in the market although at least some of said systems are equally thin.

Abstract

The invention relates to transdermal therapeutic systems which have the active ingredient nicotine and have particularly high flexibility. This flexibility decisively improves wearer comfort on the skin, since the system is readily capable of adapting to the surface of the skin and its constant movement. Surprisingly, the nicotine TTS of the invention is markedly more flexible than the conventional nicotine TTS products which are leaders in the market, although at least some of those systems are comparably thin.

# Highly flexible transdermal therapeutic system with nicotine as active ingredient

## Description

### Prior art

Transdermal therapeutic systems (TTSs) comprising nicotine have been described in the market and also in many patent specifications. Examples which may be mentioned are: EP-A 708 627, EP-A 366 240, EP-A 720 474, US-A 5,364,630, WO 95/24172, WO 94/04109, WO 00/33812, WO 88/01516. Reference is also made to the current TTS products which are market leaders: Nicotinell® (Habitrol® in the US), Nicorette® (Nicotrol® in the US) and Nicoderm®.

There are two problem areas substantially determining how nicotine TTSs are developed:

1. Nicotine is very volatile. Preparation processes which encompass drying steps are therefore made difficult or impossible.
2. Nicotine is a powerful plasticizer or solvent for polymers and plastic films as typically used in the production of TTSs.

The problems in 1. have led to the development of processes in which there is no need to dry the nicotine-containing material, and there is therefore no escape of nicotine through evaporation or vaporization.

The problems in 2. have led to many descriptions of polymers and plastic films which are particularly resistant to nicotine. This applies not only to pressure-sensitive-adhesive formulations but also to the

protective and backing layers of TTSs, and also to suitable primary packaging.

All of the solutions found to these problems have hitherto been associated with some compromises with regard to complex system structure, and also in particular with regard to the thickness of the TTSs, which is sometimes considerable.

To avoid coating and drying, processes have been described for printing part or all of the surface of TTSs or individual layers thereof, but these require the presence of absorbent webs or papers. Nicotine can also be fed in liquid or thickened form into a reservoir system. However, systems of this type require considerable resources for production and are often thick and have a less than attractive appearance. Hot-melt processes may also be used, avoiding the use of solvents and making drying unnecessary. However, these imply, inter alia, considerable limitations in the selection of the polymers and auxiliaries. The plasticizing properties of nicotine have proven to be particularly problematic for the use of pressure-sensitive acrylate adhesives, since these have a relatively low glass transition temperature even when pure, this being the basis for their high spontaneous adhesion to human skin. Even with low concentrations of nicotine, therefore, a critical soft consistency arises and results in streaking and stringing, and very generally to problems with handling of the adhesive films, either on machines or manually.

For this reason, the systems proposed hitherto in connection with pressure-sensitive acrylate adhesives have almost exclusively had a particularly thick multilayer structure, each being required to absorb only

a relatively low concentration of nicotine. Although the acrylate group also permits the selection of relatively high-molecular-weight products whose greater molecular weight gives them greater resistance to plasticizing substances such as nicotine, these can only be processed by the hot-melt process, and the selection of acrylates of this type available specifically for pharmaceutical applications rather than solvent-based pressure-sensitive adhesives is very restricted. In this context, there have hitherto been many systems proposed based on other polymers less sensitive to nicotine, e.g. hydrocarbon polymers, such as polyisobutylene or polybutylene, or else block copolymers of styrene with isoprene or butadiene. Silicone polymers have also been proposed, but of all the polymers available these are easily the most expensive. Finally, the systems marketed have marked differences in size for the same dispensing rate, this again being the result of the different resistances of the systems to the amount of nicotine present.

A general rule is that nicotine-resistant polymers have relatively high molecular weight and/or should have a glass transition temperature which is relatively high for pressure-sensitive adhesives. Among the polymers commonly used for producing TTSs, this consideration is least applicable to pressure-sensitive acrylate adhesives which can be processed using solvents.

In summary, it may be said that when compared with conventional matrix systems with other active ingredients (e.g. estrogen), the nicotine TTSs currently marketed are of unusually thick and stiff design, for the abovementioned reasons. With system areas of from 20 to 30 $cm^2$, this considerably reduces wearer comfort.

Invention

The object of the present invention was to provide a thin and highly flexible nicotine TTS which has considerably better wearability than conventional nicotine TTSs. The structure of the system should moreover be very simple, and it should be possible to use a solvent-containing coating for its production.

The invention achieves this object by means of a transdermal therapeutic system which comprises nicotine and, where appropriate, other active ingredients and/or auxiliaries which act on the central nervous system, and is composed of a backing layer (1) impermeable to nicotine and to the other active ingredients and auxiliaries, and preferably also to water vapor, of a nicotine-containing intermediate matrix layer (2) immediately adjacent to the backing layer, of another nicotine-containing matrix layer (3), and of a peelable protective film (4), wherein all of the matrix layers are composed of (meth)acrylate copolymers which can be processed in solvent-containing systems, and where the total thickness of these layers (i.e. only the matrix layers together with the backing layer, i.e. excluding the protective film (4)) does not exceed 250 µm. The (meth)acrylate copolymers used in the transdermal therapeutic systems of the invention are therefore exclusively those capable of being processed in solvent-containing systems, and there is no need for any strengthening layers made from foreign polymers, or for reinforcement, such as paper or nonwoven.

The term (meth)acrylate copolymers used here means copolymers made from acrylates and/or from methacrylates, i.e. alkyl esters whose alkyl radical advantageously has

from 1 to 8, preferably from 1 to 6, in particular from 1 to 4, carbon atoms. Copolymers of this type may also be prepared with concomitant use of vinyl acetate, acrylic acid, and/or methacrylic acid. The property "capable of being processed in solvent-containing systems" implies that the (meth)acrylate copolymers have sufficient solubility or swellability in organic solvents to permit them to be cast without difficulty. (Meth)acrylate copolymers which have this capability are preferably those whose molecular weight is not above about 400 kDa. It is impossible to allocate a strict limit here, since the solubility of (meth)acrylate copolymers can be affected by adding certain auxiliaries, for example.

The nicotine loading of the transdermal therapeutic system is advantageously such that it comprises at least 1.5 mg of nicotine per $cm^2$ of application surface. The design of one advantageous embodiment of the system is such that from 0.7 to 1.4 mg, preferably from 1.0 to 1.4 mg, of nicotine is dispensed per $cm^2$ of skin within 24 hours, preferably within 16 hours.

The nicotine-containing intermediate matrix layer (2) is advantageously based on a polymer from the group of (meth)acrylate copolymers, preferably butyl methacrylate-(2-dimethylaminoethyl methacrylate)-methyl methacrylate copolymer, in particular a copolymer of this type having the molar ratio 1:2:1, or else a butyl methacrylate-methyl methacrylate copolymer.

The nicotine-containing matrix layer (3) is the pressure-sensitive-adhesive layer (adhesive layer) on the side facing the skin. This preferably has a structure based on acrylate copolymers which retain unesterified carboxy groups deriving from the acrylic or methacrylic acid and

which have an acid value of from 20 to 100 mg KOH per g of polymer, for example, and which may have been neutralized completely or partially by one or more basic additives. Copolymers of this type are particularly plasticizer-resistant and, if they have been - preferably partially - neutralized, have very good nicotine-release properties. The design of these transdermal therapeutic systems can be surprisingly thin, and the systems have astoundingly high flexibility, even when compared with competitive products which are similarly thin. Surprisingly, the invention permits the unprecedented production of nicotine TTSs which have this degree of thinness and are at the same time highly flexible, with flexural stiffness of not more than 2 cN × $cm^2$.

Examples of additives which are used with the acrylate copolymers containing carboxy groups are alkali metal hydroxides, preferably potassium hydroxide, and basic polymers, preferably the abovementioned butyl methacrylate-(2-dimethylaminoethyl methacrylate)-methyl methacrylate copolymer. In one particularly advantageous embodiment, the acrylate copolymer containing carboxyl groups has been crosslinked by aluminum ions or titanium ions.

It is advantageous for their also to be at least one strongly water-binding auxiliary present in the TTSs of the invention, preferably a polymer containing carboxy groups or its pharmaceutically acceptable salt. This is preferably an auxiliary from the group consisting of the sodium or calcium salts of crosslinked carboxymethyl-cellulose or of crosslinked polyacrylic acid, and it is advantageous for this auxiliary to be present in powder form, dispersed in one or more of the matrix layers. The content of the water-binding constituent in the matrix is

generally from 1 to 10% (w/w), preferably from 2 to 4% (w/w).

The other active ingredients and/or auxiliaries which act on the central nervous system and may be used are those previously described in the prior art in connection with nicotine for transdermal therapeutic systems, e.g. agents with stabilizing action, such as conventional antioxidants, preferably Vitamin E or ascorbyl palmitate.

Flexibility means the capability of a sheet to bend and thus adapt to an uneven surface. In practically all regions of the body, the skin is an uneven surface, all the more so since movements of the body constantly change the shape of its surface. The method for, and result of, comparative flexibility tests are described at a later stage. These also clearly show that the low flexural stiffness of not more than 2 cN × $cm^2$ is not merely a function of low system thickness but is also a function of the particularly flexible layer structure and/or of the matrix formulation. A fact which is of assistance here is that the TTSs of the invention comprise no separate active ingredient depots and no reinforcement, and no control membranes.

Compared with products available in the market, this novel formulation is at least equivalent or even superior in dispensing rate from the nicotine TTS per unit of area and time. This is demonstrated by other comparative studies, also described at a later stage in this specification.

The use of nicotine and, where appropriate, liquid auxiliaries generally means high loading of the matrix layers with plasticizing constituents. The formulations

used for the pressure-sensitive-adhesive matrix layer(s) are therefore particularly plasticizer-resistant. Examples of these are cationically crosslinkable acrylate copolymers. Partially neutralized acrylate copolymers containing carboxy groups, as described in DE-A 199 18 106, are particularly suitable.

Figure 1A shows a typical system structure for a matrix TTS of the invention. A backing layer (1), preferably impermeable to water vapor, is followed by an intermediate matrix layer (2). There is then a pressure-sensitive-adhesive matrix layer (3). The pressure-sensitive-adhesive surface of (3) has been covered by a protective film (4), which is removed before the TTS is used.

Finally, depending on the production process, a system structure as in figure 1B may also be advisable. The intermediate matrix layer (2), not covering the entire surface, is introduced using printing technology, for example. The margin of the pressure-sensitive-adhesive matrix layer (3) is in direct contact with the backing layer (1), and the layer (3) therefore forms a final external margin around the inner intermediate matrix layer (2).

Polymers suitable for thickening the volatile constituent have been specified in DE-A 43 32 094. These are preferably not pressure-sensitive-adhesive polymers, since pressure-sensitive-adhesive polymers are practically impossible to obtain commercially free from solvent and are difficult to process in pure form.

Particularly suitable polymers for the present invention have proven to be those based on methacrylic acid or on

its esters. Typical representatives of this group of polymers, such as Eudragit® grades, in particular Eudragit® E, or Plastoid® B, both products from Röhm GmbH, Darmstadt, Germany, have only modest thickening action in solution. This is desirable, since the initial polymer content of the solution can therefore be kept relatively high, generally from 20 to 40% (w/w). This permits rapid solidification of the solution to give a cohesive polymer film of adequate thickness and strength as equilibrium then becomes established. Polymethacrylates moreover have good anchoring properties on substrate webs made from polyethylene terephthalate (PET), these in turn being the preferred material for backing layers of TTSs.

Besides the polymer present, other auxiliaries may be added if required to reduce the content of active ingredient in the nicotine solution used. This can be advisable for adjustment of the amount of nicotine introduced into the system per unit area, or else to adjust to a suitable viscosity for coating with this solution. Additives of this type may also improve adhesion and, once the system has reached equilibrium, increase the bond strength between the separate layers in the composite. Without making any claim to completeness, some preferred additives are: triglycerides of saturated fatty acids (e.g. Miglyol® 812) (a mixed acid triglyceride from fractionated coconut fatty acids from the company Degussa, Germany), monoglycerides of fatty acids (e.g. glycerol monolaurate or glycerol monooleate), esters of methanol, of ethanol, of isopropanol , or of propylene glycol with fatty acids (e.g. isopropyl palmitate), and also hard or soft resins in the form of derivatives of abietic acid.

Preferred suitable materials for the backing layer of the TTS are films with low nicotine permeability. Examples of these are polyethylene terephthalate, e.g. Hostaphan® from the company Mitsubishi (PET) and thermoplastic acrylonitrile copolymers, as obtained by graft polymerization of 73-77 parts of acrylonitrile and 23-27 parts of methyl acrylate in the presence of 8-18 parts of butadiene-acrylonitrile copolymer having 70% of butadiene (parts and percentages in each case being based on weight), marketed with the name Barex® (previously: trademark of the company Vistron Corp., Cleveland, Ohio, USA; now BP). (Cf. M. Th. Schuler in Kunststoffe-Plastics, 9/1974, pp. 13-20). These films may have been provided with a surface finish for cosmetic reasons. If required, aluminum may have been applied to protect the nicotine-containing matrix layers from light.

Comparative flexibility tests

To allow objective assessment of this product quality feature, which is very easily perceived by the user, the DIN 53 362 method of determining flexural stiffness (cantilever method) for plastic films and sheet textiles was adapted, utilizing for this purpose test equipment complying with the standard and obtained from the company Richard Hess MBV GmbH, 47663 Sonsbeck, Germany. The principle here is that a specimen strip of the product to be tested is advanced by way of an edge freely into space. As the length of the overhang increases, the sheet bends downward under its own weight. The overhang length at which a prescribed angle of flex of 41°30' is reached is recorded and converted by calculation into a value which measures flexural stiffness in the unit [cN × $cm^2$] as a function of the weight of the specimen.

The test specimens used were strips cut out from finished TTSs. The length of the test specimens here had to be restricted to the available length of the commercial products, deviating from the prescribed length of 250 mm in the DIN specification (the actual lengths of the test specimens being from 40 to 70 mm). The protective film for the adhesive layer was removed from the test specimens prior to the test. In accordance with the abovementioned DIN specification, the adhesive layer was covered with talcum powder until it was no longer tacky.

The test results (average from n = 2 determinations) and the associated lengths of the test specimens are listed in table 1. The flexural stiffness of each test specimen was determined in both directions, i.e. with the backing layer upward for the first test and with the backing layer facing downward for the second test. This took account of the fact that a TTS should typically be flexible in both directions when worn on the skin. A novel nicotin TTS of the invention as in example 1 was compared with three marketed nicotine TTSs, and moreover with 2 marketed estradiol-containing products, which serve here as a useful reference for high flexibility and high wearer comfort.

Table 1:

| | **Nicotine TTS A** | **Nicotine TTS B** | **Nicotine TTS C** | **Inven-tion*** | **Estradiol TTS E** | **Estradiol TTS F** |
|---|---|---|---|---|---|---|
| Flexural stiffness direction A | > 14.5 cN × $cm^2$ | > 8.9 cN × $cm^2$ | n.a. | 1.4 cN × $cm^2$ | 1.16 cN × $cm^2$ | 0.94 cN × $cm^2$ |
| Flexural stiffness direction B | > 14.5 cN × $cm^2$ | > 8.9 cN × $cm^2$ | 3.33 cN × $cm^2$ | 1.16 cN × $cm^2$ | 0.27 cN × $cm^2$ | 0.8 cN × $cm^2$ |
| System thickness without protective film | 238 µm | 389 µm | 394 µm | 218 µm | 110 µm | 117 µm |

*Nicotine TTS of the invention produced as in example 1 below.

n.a.: not applicable since test specimen formed a roll

Nicotine TTS A refers to the product Nicorette®, a trademark of Pharmacia & Upjohn GmbH, Nicotine TTS B to Nicoderm® CQ, a trademark of SmithKline Beecham Consumer Healthcare L.P. (USA), Nicotine-TTS C to Nicotine Transdermal USP, marketed by Schein Pharmaceutical, Inc. (USA). Estradiol TTS E refers to Dermestril®, a trademark of the company Rottapharm s.r.l. (Monza, Italy), and Estradiol TTS F to Fem7®, a trademark of Merck KGaA, Darmstadt, Germany.

Direction A implies that the backing layer of the TTS is facing downward when the test specimen is tested, while the backing layer is upward for testing in direction B.

In some cases excessive stiffness meant that it was impossible to achieve the angle of flex of 41°30' from the test specimens in the length available.

In those cases it was assumed that the result has to be greater than the value which would have been calculated if the critical angle had been reached using the overhang length possible with the test specimen.

In the case of nicotine TTS C, the product had a marked tendency to form a roll or to curl. This made it impossible to test in direction A. It was possible to utilize only the values measured in direction B.

The values measured show that the nicotine TTS of the invention has markedly lower flexural stiffness than the comparative TTSs using nicotine as active ingredient. Indeed, surprisingly, the values are in the region of those from two single-layer thin matrix TTSs with estradiol as active ingredient. These are among the most flexible TTSs in the current market.

Surprisingly, the flexural stiffness of the nicotine TTS of the invention is also very markedly below that of nicotine TTS A. There is only insignificant difference between the thicknesses of the two systems (nicotine TTS A about 238 µm, nicotine TTS of the invention about 218 µm)

Example 1

DE-A 43 32 094 discloses products and processes which permit the introduction of volatile pharmaceutical active ingredients or auxiliaries into TTSs. To this end, the volatile constituent is thickened by dissolving a polymer and, where appropriate, other solid auxiliaries in the volatile constituent as solvent in such a way that this solution can be coated onto a substrate web (= process step 1). This coated product is then laminated to other separately produced layers of the TTS, and then the

volatile substance can reach equilibrium in the entire system through diffusion (= process step 2). The layer which was previously liquid solidifies there by diffusion of the volatile constituent, which is the only solvent, into the other layers of the TTS.

The composition of the polymer solution for process step 1 is as in table 2. An application system is used to coat this over the surface of a film made from polyethylene terephthalate of thickness 19 µm, the weight per unit area used being 54 g/m$^2$. The coated product is immediately laminated, in process step 2, to a pressure-sensitive-adhesive layer of composition as shown in table 3 and of thickness 144 g/m$^2$. The resultant product is heated to 60°C for 10 minutes and then wound up onto a roll. This product is further processed in a conventional manner, immediately or else after intermediate storage, by longitudinal cutting and stamping to give TTSs.

Table 2:

| **Description** | **Amount [%]** | **Function** |
|---|---|---|
| Nicotine | 32.41 | Volatile active ingredient |
| Eudragit® EPO | 27.00 | Methacrylate copolymer thickener |
| Miglyol® 812 | 40.23 | Auxiliary |
| Vitamin E | 0.36 | Antioxidant |

Table 3:

| **Description** | **Amount [%]** | **Function** |
|---|---|---|
| Durotak® 387-2051 | 95.18 | Pressure-sensitive acrylate copolymer adhesive |
| KOH | 0.77 | Neutralizing reagent |
| Aluminum* | 0.05 | Crosslinking reagent for Durotak |
| Sodium salt of crosslinked carboxymethylcellulose | 4.00 | Hydroadsorbent |

* The aluminum is used in the form of Al acetylacetonate.

The adhesive layer as in Table 3 is produced by a conventional coating process in a solvent-containing system, followed by drying. The solvent used was a mixture of ethyl acetate, methanol, and acetylacetone. The coating took place onto a siliconized protective film made from polyethylene terephthalate (100 µm Hostaphan® film).

The resultant TTS has about 1.75 mg of nicotine active ingredient content per $cm^2$ of application surface. This corresponds very closely to the content in nicotine

TTS D. However, the thickness of the system of the invention is only about 218 µm (determined without protective film) and is therefore below that of the abovementioned systems.

Comparative pharmacokinetic studies

The inventive nicotine TTS of example 1 was compared with a nicotine TTS D (Nicotinell® TTS from Novartis Consumer Health Care S.A., Basle, Switzerland) in a pharmacokinetic study on humans (6 healthy male subjects using the inventive and the comparative preparation in succession - crossover design). The areas under the plasma level curve in figure 2 demonstrate superiority of the inventive nicotine TTS of the order of 140%, based on TTSs of identical area. This corresponds to a dispensing rate of about 1 mg of nicotine per $cm^2$ in 24 hours, whereas the value declared for nicotine TTS D is 0.7 mg per $cm^2$ in 24 hours.

A comparison was also made in vitro with nicotine TTS A. Permeation rates were determined on human skin in modified Franz diffusion cells commonly used for this purpose. The test temperature was 32°C, and an aqueous buffer of pH 5.5 was used as acceptor medium. All of the data are average values from n=3 specimens of skin from the same donor, determined using stamped TTS sections of area 1.12 $cm^2$. The results presented in figure 3 show the superiority of the inventive nicotine TTS over nicotine TTS A with respect to the total amount of nicotine dispensed per $cm^2$ in 24 hours.

Example 2

EP-B 0 303025 discloses a printing process with which nicotine can be introduced into each TTS. With the aid of

this principle and printing equipment from the company Tampoprint, round areas of the active ingredient solution as in table 4 were applied by direct printing over the surface of a pressure-sensitive-adhesive layer whose composition was as in table 5, printing about 25 mg of nicotine solution onto an area of about 6 $cm^2$ of adhesive. The weight per unit area for the pressure-sensitive-adhesive layer as in table 5 was 144 $g/m^2$.

After print-application, the printed adhesive layer was immediately covered with a backing layer made from polyethylene terephthalate (15 µm Hostaphan film), to which it was mechanically laminated. The printed areas were stamped out from this composite using a round stamping tool. The diameter selected here for the stamped section was greater by about 4 mm (corresponding to about 8 $cm^2$ in area) than the diameter of the printed area. A system as in Figure 1B was thus produced. On storage, nicotine equilibrium became established within all of the layers of the TTS.

Table 4:

| **Description** | **Amount [%]** | **Function** |
|---|---|---|
| Nicotine | 60.00 | Volatile active ingredient |
| Eudragit® 100 | 40.00 | Methacrylate copolymer thickener |

Table 5:

| **Description** | **Amount [%]** | **Function** |
|---|---|---|
| Durotak® 387-2051 | 85.26 | Pressure-sensitive acrylate copolymer adhesive |
| KOH | 0.69 | Neutralization reagent |
| Aluminum* | 0.05 | Crosslinking reagent for Durotak |
| Sodium salt of crosslinked carboxymethylcellulose | 4.00 | Hydroadsorbent |
| Eudragit E 100 | 10.00 | Basic auxiliary |

* The aluminum was added in the form of Al acetylacetonate.

The adhesive layer as in Table 5 is produced by a conventional coating process in a solvent-containing system, followed by drying. The solvent used was a mixture of ethyl acetate, methanol, and acetylacetone. The coating took place onto a siliconized protective film made from polyethylene terephthalate (100 µm Hostaphan® film).

Patent Claims

1. Transdermal therapeutic system with nicotine content, composed of a backing layer impermeable to nicotine, of a nicotine-containing intermediate matrix layer immediately adjacent to the backing layer, of another nicotine-containing matrix layer, and of a peelable protective layer, where the matrix layers are composed of (meth)acrylate copolymers, wherein the total thickness of these layers does not exceed 250 µm and the nicotine content is at least 1.5 mg per $cm^3$ of application surface.

2. The transdermal system in particular as claimed in claim 1, wherein the flexural stiffness of the laminate to be applied to the skin is not more than 2 cN × $cm^2$.

3. The transdermal system as claimed in claim 1 or 2, which is free from supports and strengthening layers.

4. The transdermal system as claimed in one or more of the preceding claims, which is intended for dispensing from 0.7 to 1.4 mg, preferably from 1.0 to 1.4 mg, of nicotine per $cm^2$ of skin within 24 hours, preferably for an application time of 16 hours.

5. The transdermal system as claimed in one or more of the preceding claims, wherein the intermediate layer is based on a polymer from the group consisting of methacrylate copolymers, preferably butyl methacrylate-(2-dimethylaminoethyl methacrylate)-methyl methacrylate copolymer or a butyl

methacrylate-methyl methacrylate copolymer.

6. The transdermal system as claimed in one or more of the preceding claims, wherein the pressure-sensitive-adhesive layer on the side facing the skin has a structure based on acrylate copolymers.

7. The transdermal system as claimed in one or more of the preceding claims, wherein the pressure-sensitive-adhesive acrylate copolymer contains carboxy groups and is advantageously present in a form completely or partially neutralized by one or more basic additives and/or in a form crosslinked by aluminum ions or titanium ions, and the basic additive is preferably an alkali metal hydroxide, in particular potassium hydroxide, or a basic polymer, butyl methacrylate-(2-dimethylaminoethyl methacrylate)-methyl methacrylate copolymer (1:2:1).

8. The transdermal system as claimed in claim 7, wherein at least one strongly water-binding auxilary present in the system and is preferably a polymer containing carboxy groups or its pharmaceutically acceptable salt.

9. The transdermal system as claimed in one or more of the preceding claims, wherein the (meth)acrylate copolymers of which the matrix layers are composed can be processed in solvent-containing systems.

10. The transdermal system as claimed in one or more of the preceding claims, wherein at least one other active ingredient and/or auxiliary which acts on the central nervous system is present.

Fig.1A

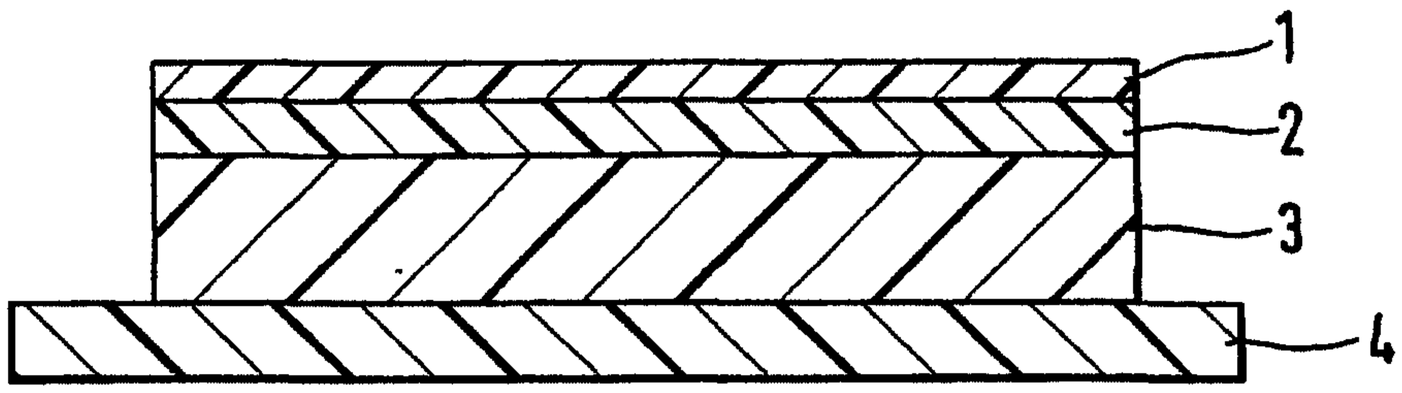
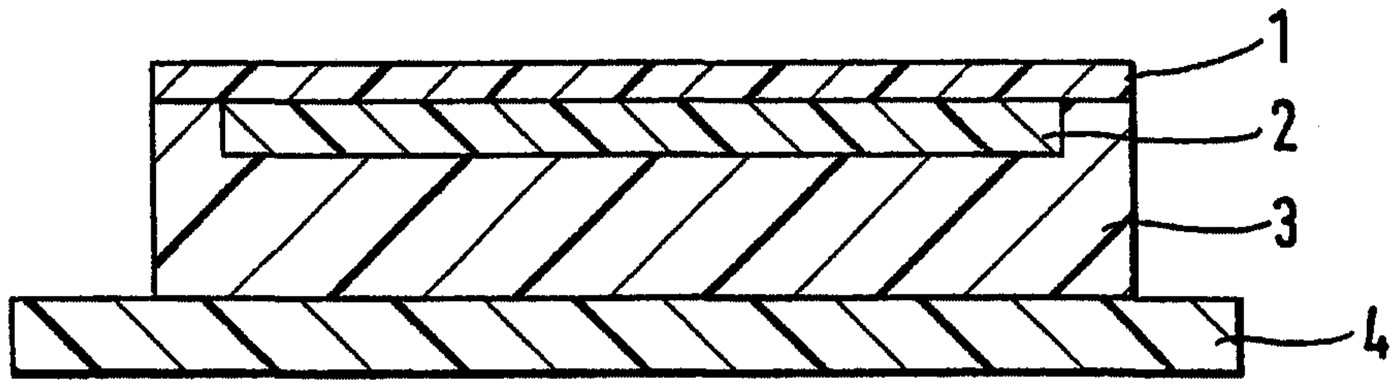



Fig.1B



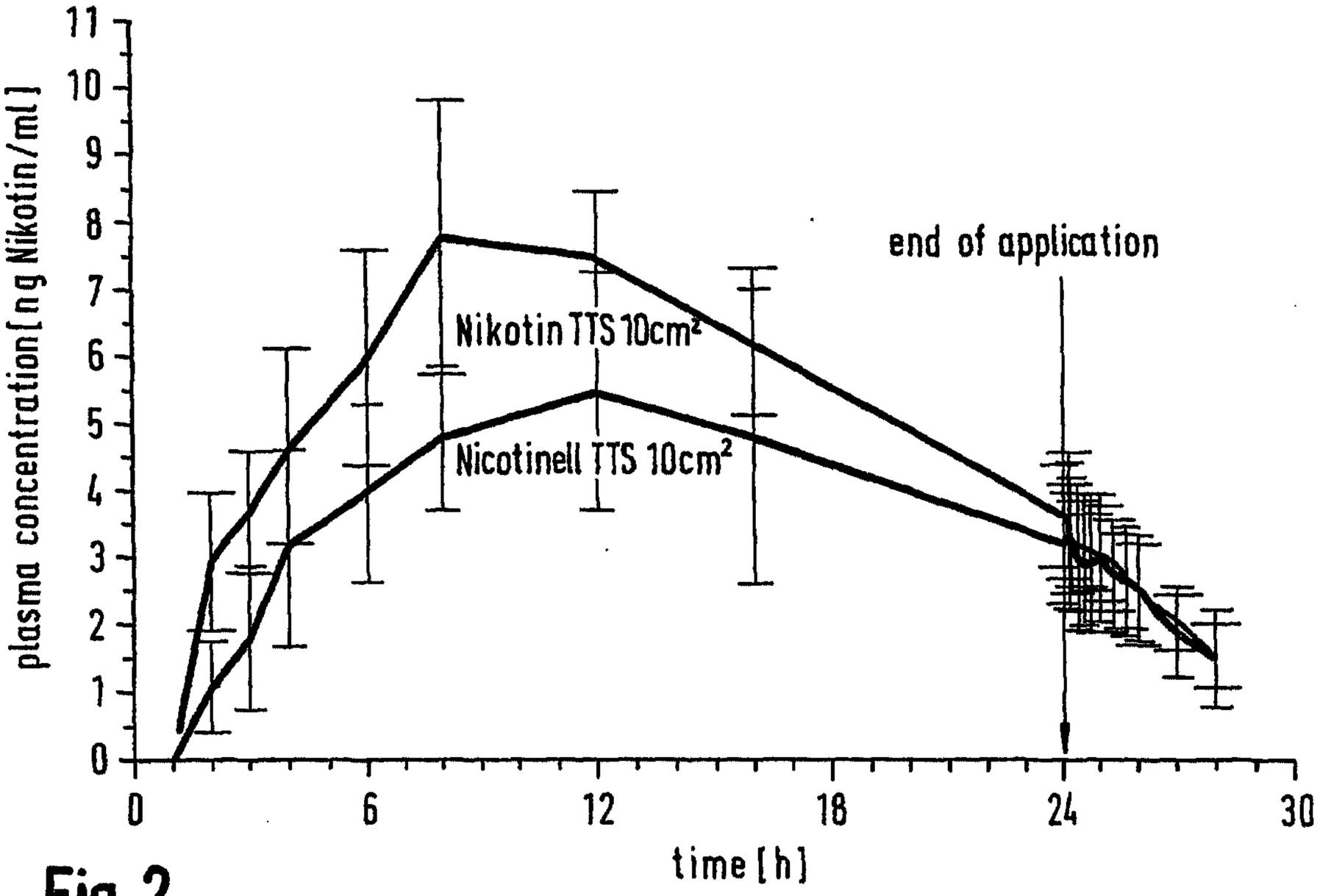

plasma concentration [ng Nikotin/ml]
11
10
9
8
7
6
5
4
3
2
1
0
0
6
12
18
24
30
time [h]
end of application
Nikotin TTS 10cm²
Nicotinell TTS 10cm²

Fig.2


Nikotin Permeation [µg/cm²]
600
550
500
450
400
350
300
250
200
150
100
50
0
0
4
8
12
16
20
24
28
time [h]
Nicorette TTS
Nikotin TTS

Fig.3